Study of Serum Cystatin C in Relation to Cardiovascular Morbidity in Type ٢ Diabetes Mellitus (Non Insulin Dependant Diabetes Mellitus) in Patients without Diabetic Nephropathy

Thesis

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By:

Mahmoud Fathy Hashem

Diploma of internal medicine

Supervised by

Prof. Dr. Mohamed Ali Ibrahim

Professor of Internal Medicine and Nephrology
"Chair Person of Nephrology Department"
Faculty of Medicine, Ain Shams University

Prof. Dr. Dawlat Hussien Sany

Assistant professor of Internal Medicine and Nephrology
Faculty of Medicine, Ain Shams University

Dr. Essam Nour El-Din Afiffy

Lecturer of Internal Medicine and Nephrology
Faculty of Medicine, Ain shams University

Faculty of Medicine
Ain Shams University

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بسم الله الرحمن الرحيم
قالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ
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Mahmoud Fathy

Contents

List of Abbreviations

ACE	:	Angiotensin-converting enzyme
AGE	:	Advanced glycosylation end products
AKI	:	Acute kidney injury
ARBs	:	Angitensin receptor blockers
ATN	:	Acute tubular necrosis
BMI	:	Body mass index
BTP	:	B-Trace Protein
C.G	:	Cockcroft and Gault
CBC	:	Complete blood count
CIDP	:	Chronic Inflammatory Demyelinating Polyneuropathy
CKD	:	Chronic kidney disease
CRP	:	C-reactive protein
CSF	:	Cerebrospinal fluid
CTGF	:	Connective tissue growth factor
CVD	:	Cardiovascular Diseases
CyC	:	Cystatin C
DBP	:	Diastolic blood pressure
DK	:	Diabetic ketoacidosis
DKD	:	Diabetic kidney disease
DM	:	Diabetes Mellitus
DN	:	Diabetic nephropathy
DPG	:	Diphosphoglcerate
ERFD	:	Early renal function decline
ERK	:	Extracellular regulating kinase
ESRD	:	End-stage renal disease

List of Abbreviations (Cont.)

ET-١	:	Endothelin-١
GBM	:	Glomerular basement membrane
GBS	:	Guillan-Barre Syndrome
GFR	:	Glomerular filtration rate
GGT	:	γ-glutamyltransferase
GST	:	Glutathione S-transferase
HbA١c	:	Glycosylated hemoglobin
HCC	:	Human Cystatin C
HDL	:	High density lipoprotein
HPLC	:	High performance liquid chromatography
HSPG	:	Heparan sulfate proteoglycan
IDDM	:	Insulin dependent diabetes mellitus
IFKF	:	International Federation of Kidney Foundations
IGF	:	Insulin-like growth factor
IN	:	Immunonephelometry
IND	:	Inflammatory Neurologic Diseases
IT	:	Immunoturbidimetry
LDH	:	Lactate dehydrogenase
LDL	:	Low density lipoprotein
MDRD	:	Modified Diet in Renal Disease
NADPH	:	Nicotinamide adenine dinucleotide phosphate
NAG.	:	N-acetyl-ß-D-glucosaminidase
NIDDM	:	Non insulin dependent diabetes mellitus
OR	:	Odds ratio
PA	:	Plasminogen activator

List of Abbreviations (Cont.)

PENIA	:	Particle-enhanced nephelometric immunoassay
PETIA	:	Particle-enhanced turbidimetric immunoassay
PKC	:	Protein kinase C
PPAR	:	Peroxisome proliferator-activated receptor
RAS	:	Renin-angiotensin system
RIA	:	Radioimmunoassay
ROS	:	Reactive oxygen specie
RPF	:	Renal plasma flow
RPN	:	Renal papillary necrosis
RRT	:	Renal replacement therapy
SBP	:	Systolic blood pressure
SNPs	:	Single nucleotide polymorphisms
T١D	:	Type ١ diabetes
T٢D	:	Type ٢ diabetes
TGF-β	:	Transforming growth factor- β
TNF-α	:	Tumor necrosis factor-α
UAE	:	Urinary albumin excretion
UTI	:	Urinary tract infection
VEGF	:	Vascular endothelial growth factor

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Introduction

Diabetes mellitus is one of the most important health issues facing the world in the ٢١st century. Many of the complications of diabetes are cardiovascular in nature. Patients with type.٢ and prediabetics are at risk of developing macrovascular and microvascular complications including: atherosclerosis, coronary heart disease cardiomyopathy, cerebrovascular stroke, transient ischemic attacks, peripheral neuritis,. renal failure, retinopathy and peripheral vascular insufficiency **(Hanefeld M, ٢٠٠٧).**

Cardiovascular risks increase among patient with chronic kidney disease **(Go as et al, ٢٠٠٤).** Patients with chronic kidney disease (CKD), irrespective of diagnosis arc at increased risk of cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure.

Since inflammation plays an important role in atherogenesis and development of cardiovascular disease, C-reactive protein (CRP) has been intensively investigated as potential marker of atherosclerosis and cardiovascular morbidity. However, its role in clinical setting is still debated **(Pinon P and Carlos J, ٢٠٠٦).**

Cystatin C is a non-glycosylatecl basic protease inhibitor that is produced at a constant rate by all nucleated cells. It is freely filtered by the renal glomerulus and primarily catabolized in the renal tubules **(Newman DJ, ٢٠٠٢)**. Levels are reported to be independent of gender, age, and body mass. The serum concentration of cystatin C has recently been proposed as an endogenous marker of renal function that is more reliable than serum creatininc and accurate even at the low concentrations found whether glomerular filtration rate (GFR) is normal or elevated **(Pussi L et al, ٢٠٠٧)**.

There is growing evidence suggesting that increased cystatin C concentrations are strongly and independently associated with future cardiovascular events in individuals with high risk. Whether this is exclusively related to cystatin C's ability to accurately asses renal function or is influenced by other factors that may modulate the level of this protein in blood is still a matter of controversy **(Bard JM et al, ٢٠٠٦)**.

Aim of the Work

Is to study the possible value of serum cystatin C level as predictor of cardiovascular risks and morbidity in type, ٢ diabetes mellitus in patients without diabetic nephropathy.

Chapter ١

Kidney Diseases of Diabetes

Chronic kidney disease (CKD) is an international public health problem affecting ٥٪ to ١٠٪ of the world population **(KDIGO, ٢٠٠٩)**. Diabetes mellitus (DM) causes CKD and accelerates its progression, and is recognized as the leading cause of end-stage kidney disease (ESKD) **(Kasper and Harrison ٢٠٠٥; KDOQI., ٢٠٠٧; Toto, ٢٠٠٢).**

CKD associated with DM, often called diabetic kidney disease (DKD), occurs in ٣٠٪ to ٤٠٪ of type ١ diabetic patients and in an increasing percentage (up to ٢٥٪) of type ٢ patients **(Ritz et al., ١٩٩٩).** The percentage of people with DKD has increased more than for any other cause of CKD, increasing by ١٠٪per year over the last decade **(Collins et al., ٢٠٠٥; Ritz et al., ١٩٩٩)** and the increase is predominantly in those with type ٢ diabetes. The population of existing patients whose ESKD was caused by diabetes (tripled from ١٩٩٠ to ٢٠٠٠) is expected to grow ١٠-fold by ٢٠٣٠, to ١,٣ million **(Collins et al., ٢٠٠٥).**

In the USA, diabetes now accounts for ٤٥٪ of prevalent kidney failure, up from١٨٪in ١٩٨٠ **(KDOQI., ٢٠٠٧).** DM and CKD are common and exhibit synergistic associations with premature mortality in the general population **(Middleton et al., ٢٠٠٦).**